Reducing Non-Anastomotic Biliary Strictures in Donation After Circulatory Death Liver Transplantation: Cold Ischemia Time Matters!

To the Editor:

We were impressed to read about the beneficial effect of preimplantation Hypothermic Oxygenated PErfusion (HOPE) on the outcome after transplantation of livers donated after circulatory death (DCD).[1] In an internationally matched cohort study, Dutkowski et al showed that HOPE reduces postreperfusion graft injury and early allograft dysfunction compared with conventional static cold storage. Furthermore, HOPE was associated with a lower incidence of ischemic cholangiopathy, also called non-anastomotic strictures (NAS), and 1-year graft survival.

Warm ischemia time (WIT) is currently widely accepted as a risk factor of NAS,[2–4] but recent findings suggest that the detrimental effect of prolonged cold ischemia time (CIT) on the biliary tree and graft function should not be underestimated.[5–7] We wonder whether (part of) the effect on NAS in the treatment group might not be due to the very short CIT in the HOPE livers and the observed difference with the DCD control group [HOPE-DCD 3 hours (188 minutes) vs DCD 6.5 hours (395 minutes); $P = 0.01$]. The authors report overall graft and cholangiopathy-free graft survival 1 year after transplantation, and Cox regression was corrected for CIT. However, as only 1 hazard ratio is given, it is not clear to us that the HOPE effect on cholangiopathy-free graft survival in multivariate regression was indeed independent of CIT. Additionally, it would be valuable to know whether CIT was also an independent factor of NAS in this series, as that gives useful information for current clinical practice in which DCD livers are mostly still statically cold stored.

We ask the question since we observed NAS developing in our DCD recipients despite very short asystolic WIT (defined as the period of time between circulatory arrest and cold flush in situ), indicating that indeed other factors are at play. In a retrospective analysis of 61 DCD liver transplantations performed in our institution between 2003 and 2013, we could show a considerable role of CIT. Donor, recipient, operative, and outcome data were compared between recipients with NAS (NAS+) and those without NAS (NAS−). Backward stepwise logistic regression was used to identify risk factors of NAS developing within 1 year after transplantation. Continuous data are expressed as median [interquartile range (IQR)]. Analyses were performed in SPSS 20.0, and $P < 0.05$ was considered significant. Thirteen out of 61 (21%) recipients developed NAS despite short asystolic WIT [9 minutes (8–11)] and CIT [5.8 hours (5.1–7.1)], with the shortest CIT being 3.9 hours. Asystolic WIT was similar within the groups [NAS+ 9.5 minutes (8–10) vs NAS− 8 minutes (8–10.5); $P = 0.2$]. Donor demographics did not differ with the exception of higher donor risk index in NAS+ [3 (2.9–3.5) vs 2.7 (2.4–3.1); $P = 0.03$]. No difference in recipient age, sex, indication for transplantation, Lab Model for End Stage Liver Disease (MELD) score [NAS+ 14 (11–18) vs NAS− 15 (12–20); $P = 0.8$] or Balance of Risk (BAR) score [NAS+ 2 (2–4) vs NAS− 2 (2–4); $P = 0.9$] was observed. NAS+ had longer CIT [7.3 hours (5.95–8.5) vs 5.6 hours (4.97–6.75); $P = 0.004$] and implantation time [55 minutes (46.5–60.5) vs 46 minutes (42–52.5); $P = 0.04$]. In multivariable regression, corrected for asystolic WIT and implantation time, only CIT was associated with NAS [odds ratio (OR) 1.62, 95% confidence interval (CI) 1.08–2.4, $P = 0.02$). We could identify a cut-off of 5 hours CIT as the best predictor of NAS with 100% sensitivity and 75% specificity (c-statistic of the receiver operator characteristic curve: 0.76, 95% CI 0.63–0.896, $P = 0.004$). Our data confirm that limiting the duration of CIT reduces the risk to develop NAS. In our experience and in line with previous research,[8] no biliary complications were observed in 12 recipients of DCD grafts with CIT less than 5 hours. In the series by Dutkowski et al, the upper quartile of CIT in HOPE-treated livers was 4.4 hours (264 minutes), hence almost all livers were exposed to CIT of less than 5 hours. With this premise, it is not unthinkable that DCD livers perfused with HOPE may have suffered a milder biliary injury, reducing the pretreatment probability of developing NAS. It will be very interesting to see the outcome of the ongoing multicenter randomized controlled trial in the DCD population (NCT02584283), where CITs are likely to be longer, because not all HOPE-treated grafts will be procured locally like in the study by Dutkowski et al.

We congratulate the authors on their pioneering work and thank them for any additional data they may wish to share.

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Disclosure: The authors have received no funding for this letter. There are no conflicts of interest to declare.

ISSN: 0003-4932/14/26105-0821
DOI: 10.1097/SLA.0000000000001949